

Exhibit 11

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSIA DIAGNOSTICS
Petitioner

v.

ISIS INNOVATION LIMITED
Patent Owner

CASE IPR2012-00022
Patent 6,258,540

ISIS INNOVATION LIMITED'S PRELIMINARY PATENT OWNER
RESPONSE PURSUANT TO 37 C.F.R. §42.107(a)

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I. Introduction

The Board should not institute *inter partes* review (IPR) because (1) Ariosa's Petition is procedurally improper, and (2) even if Ariosa's Petition were not procedurally improper, Ariosa is not reasonably likely to prevail in proving that any claim of the '540 patent is unpatentable.

Patent Owner Isis Innovation first (i) shows that Ariosa lacks standing because it filed a civil action challenging the validity of the '540 patent before it filed the Petition, and (ii) shows Ariosa's Petition is improperly based on Title 35 Section 101. (Section II.) If the Board agrees that Ariosa initiated a civil action challenging the validity of the '540 patent or that the Petition is improperly based on Section 101, IPR must not be instituted. Alternatively, the Board should strike and not consider Ariosa's arguments rooted in Section 101.

Second, Isis provides an overview of the relevant technology so the Board can better understand the substantive issues involved in the Petition. (Section III.)

Third, Isis shows that Ariosa's Petition (i) relies upon asserted references that are not prior art to the '540 patent and (ii) is premised on an unreasonably broad claim interpretation that ignores at least one material, recited claim step. (Sections IV & V.)

Fourth, Isis shows that Ariosa cannot prevail on any of its proposed grounds of unpatentability. (Section VI.) Ariosa's unpatentability grounds fail to establish

anticipation or *prima facie* obviousness for several reasons. Ariosa's grounds A and B fail because Lancet 1997 (i) is not prior art, (ii) can be removed under *In re Katz*, or (ii) can be sworn behind. Its ground C fails because Kazakov does not expressly or inherently disclose either recited claim step. Ariosa's grounds D and E fail because Ariosa did not establish that Schallhammer and Gocke are prior art and because Ariosa's positions are legally and factually flawed.

Finally, even if Ariosa had established *prima facie* obviousness, significant secondary considerations weigh heavily in favor of the nonobviousness of the claimed method. (Section VII.)

II. Ariosa's Petition is procedurally improper.

Ariosa's Petition is procedurally improper for two reasons. First, the Petition is barred by 35 U.S.C. § 315(a) because Ariosa filed a civil action challenging the validity of the '540 patent before it filed the Petition. Second, Ariosa's Petition is improper because it raises Section 101 issues of patent-eligible subject matter even though IPRs may only be based on Section 102 and 103 challenges involving patents or printed publications. Because Ariosa's Petition is procedurally improper, the Board should not institute *inter partes* review. Alternatively, the Board should strike Ariosa's Section 101 arguments and not consider them in deciding whether to institute *inter partes* review.

A. Ariosa lacks standing to initiate an IPR against the '540 patent.

The Board should not institute *inter partes* review because Ariosa is barred statutorily from filing its Petition challenging the patentability of the '540 patent. The Patent Act's Section 315(a)(1) prohibits the filing of a petition for *inter partes* review if, before the date on which such a petition is filed, the petitioner has "filed a civil action challenging the validity of a claim of the patent." Ariosa has done just that; it has filed a declaratory-judgment action against Sequenom (the exclusive licensee of the '540 patent) in which it is challenging the validity of the '540 patent by asserting an affirmative defense of patent invalidity. On its face, Section 315(a) bars Ariosa's Petition. And the relevant legislative history supports the plain reading of the statute that the present Petition is barred. Allowing Ariosa to proceed with this IPR while it simultaneously challenges the patent's validity in a previously-filed district-court case would violate Section 315(a) and run counter to the Congressional purpose in creating IPRs: to avoid district-court patent-invalidity litigation by providing a faster, less costly alternative at the Patent Office.

1. Relevant Facts

On December 19, 2011, Ariosa filed a civil action against Sequenom, the exclusive licensee of patent owner Isis's '540 patent and a real party in interest in this proposed *inter partes* review, in U.S. District Court for the Northern District of

California seeking “a declaration that no activities relating to Aria’s non-invasive pre-natal test using cell-free DNA circulating in the blood of a pregnant woman ... do or will ... infringe any claim of ... the ’540 patent...” Ex. 2002 at 1.^{1,2} Sequenom counterclaimed for infringement of the ’540 patent against Ariosa. Ex. 2003 at 6:19-25 & 9:17-25. Ariosa answered Sequenom’s counterclaim and challenged the ’540 patent’s validity by raising an affirmative defense asserting that all claims of the ’540 patent were invalid “under 35 U.S.C. §§ 101, 102, 103, and/or 112 and general principles of patent law.” Ex. 2004 at 4:6-9. Nearly six months after Ariosa challenged the validity of the ’540 patent by raising its invalidity defense, Ariosa filed the instant IPR petition against the ’540 patent.

2. Legal Standards

Title 35 U.S.C. Section 315(a) bars an IPR when a petitioner, prior to filing its petition, has filed a civil action challenging the validity of a claim of the patent in that civil action: “An inter partes review may not be instituted if, before the date on which the petition for such a review is filed, the petitioner or real party in

¹ Aria Diagnostics, Inc. later changed its name to Ariosa Diagnostics, Inc.

² Citations will be made as follows: exhibit number at column:line (patents); exhibit number at page:column:paragraph (§) (other publications); exhibit number at paragraph (§) (declarations); exhibit number at page:line (hearing transcript); line numbers, figure numbers, and section numbers or names may also be used.

interest filed a civil action challenging the validity of a claim of the patent.” The plain language of Section 315 reduces to three elements that, if satisfied, bar IPR petitions:

- (1) the petitioner or real party in interest filed a civil action;
- (2) the civil action was filed before the date on which the petition for IPR was filed; and
- (3) the petitioner challenged the validity of a claim of the patent in the civil action.

The legislative history shows that Congress enacted this statutory bar to avoid patent-owner harassment and to further the central purpose of IPRs to provide a cost-effective alternative to district-court patent validity litigation: “[The IPR statute] would establish an adversarial inter partes review, with a higher threshold for initiating a proceeding and *procedural safeguards to prevent a challenger from using the process to harass patent owners.*” Ex. 2005 at S952:1:¶6 (statement of Sen. Chuck Grassley) (emphasis added). “These new procedures would also provide faster, less costly alternatives to civil litigation to challenge patents.” *Id.* & Ex. 2005 at S951:2:¶2 (statement of Sen. Orrin Hatch) (“The bill will also establish another means to administratively challenge the validity of a patent at the U.S. Patent and Trademark Office, USPTO—creating a cost-effective alternative to formal litigation, which will further enhance our patent system.”)

A key directive of the IPR statute is that a party initiating a patent-validity

challenge must choose a single forum. There is a single, narrow exception to this broad statutory prohibition—only if the petitioner’s patent-validity challenge is in the form of a *counterclaim* in a suit initiated by the patent owner may the petitioner file an IPR petition in spite of its prior patent-validity challenge. 35 U.S.C. § 315(a)(3).

3. Ariosa’s IPR Petition is barred by Section 315(a).

Ariosa is barred from seeking this IPR because it first initiated a civil action challenging the validity of the ’540 patent. Ariosa filed a civil action (element 1) prior to filing its IPR (element 2) in which it is challenging the validity of the ’540 patent by virtue of its affirmative defense asserting patent invalidity (element 3). Each of these elements reflects a choice made by Ariosa. Ariosa chose to initiate the district-court lawsuit. Ariosa chose to challenge the ’540 patent’s validity by raising its affirmative defense. And Ariosa chose to do all of this before it filed its IPR petition. Having chosen to challenge validity in district court, Ariosa is barred from petitioning for IPR.

That Ariosa’s patent-validity challenge is in the form of an affirmative defense and does not appear in its complaint is of no moment. Section 315’s broad bar is not premised on the validity challenge being presented in the complaint; the statute does not mention “complaint.” Instead, the statutory language is directed to a petitioner-initiated “civil action”—in other words the entire civil lawsuit—that

challenges patent validity. And there can be no dispute that Ariosa initiated the civil action.

4. The exception of Section 315(a)(3) does not apply to Ariosa's Petition.

Section 315(a)(3)'s exception to the broad prohibition against IPRs where a petitioner has previously initiated a lawsuit challenging patent validity does not permit Ariosa's Petition. Section 315(a)(3) provides that "a counterclaim challenging the validity of a claim of a patent does not constitute a civil action challenging the validity of a claim" and therefore would not bar an IPR. This exception cannot apply to Ariosa because it has not filed any counterclaim in the district-court litigation that it initiated against the '540 patent. Ariosa could only have brought a counterclaim if Isis and Sequenom had initiated the civil action. Thus, Ariosa's counsel's statement during the parties' November 16 hearing with the Board that "invalidity is at issue [in Ariosa's civil action] only by virtue of a counterclaim" is plainly incorrect. Ex. 2001 at 10:20-21.

By choosing to raise a validity challenge as an affirmative defense in a civil action it initiated, Ariosa is plainly outside the scope of Section 315(a)(3). The canon of statutory interpretation "the express mention of one thing excludes all

others”³ requires this result. If Congress had intended an additional exception for affirmative defenses of patent invalidity, comparable to the exception for counterclaims, Congress would have created one.

5. Ariosa’s reading of the statute would render Section 315(a)(1) meaningless.

If a petitioner’s affirmative invalidity defense raised in response to a patent owner’s counterclaim of infringement does not bar IPR, a petitioner desiring to initiate multiple proceedings or harass a patent owner could simply follow the roadmap Ariosa seeks to establish in this case. A counterclaim of infringement is compulsory when a declaration of non-infringement is asserted. If it is not made, it is waived. *Capo, Inc. v. Dioptics Med. Prods.*, 387 F.3d 1352, 1356 (Fed. Cir. 2004) (“In an action for declaration of non-infringement, a counterclaim for patent infringement is compulsory and if not made is deemed waived.”) (citation omitted). Thus, rather than bring a civil action for a declaration of invalidity, a challenger will simply file a civil action for a declaration of non-infringement, knowing that the patent owner *must* counterclaim for infringement, or waive its right to assert its patent. In response to the compulsory counterclaim, the challenger then challenges validity by asserting its affirmative defenses, and

³ *Leatherman v. Tarrant County Narcotics Intelligence & Coordination Unit*, 507 U.S. 163, 168 (U.S. 1993) (“*Expressio unius est exclusio alterius*”).

315(a)(1) is effectively skirted under Ariosa's proposed scheme. If the Board were to allow an IPR petition in such a situation, it would constitute an end-around contrary to the letter and spirit of the statute.

6. The Board should not institute an *inter partes* review.

When a patent challenger picks a fight, it must elect a single forum for that fight. Ariosa chose the United States District Court for the Northern District of California as the forum to litigate all patent invalidity challenges. As a result, Ariosa is now barred from petitioning for an IPR—a second challenge initiated by Ariosa to the '540 patent. The Board should deny Ariosa's Petition because it is barred by Title 35 Section 315(a)(1). The interests of justice demand that an IPR should not be instituted.

B. Ariosa has improperly requested *inter partes* review based on Section 101's standard for subject-matter eligibility.

Ariosa's Petition improperly requests an IPR based on Section 101: "the claims of the '540 patent are invalid for the [sic] at least the following separate and independent reasons ... (iv) under *Mayo v. Prometheus* the only aspects of the independent claim that can be afforded patentable weight encompass then-conventional steps such as blood fractionation and PCR...." Petition at 6. Throughout its Petition, Ariosa relies on *Prometheus* to argue that the Board should (i) find that aspects of the '540 patent's claims cover laws of nature and, (ii) ignore those aspects in deciding whether the claim is patentable over the prior art.

Petition at ii:26-27; 4:16 to 5:7; 6:4 to 6:5; 6:12 to 6:14; 30:1 to 32:10; 34:17 to 36:17; 37:8-10.

Ariosa's approach is improper and legally flawed. It is improper because it asks the Board to decide Section 101 issues in an IPR, which is prohibited by statute. And it is legally flawed because *Prometheus*'s holding and its analysis have no relevance to patentability under Sections 102 and 103. Because the *Prometheus* arguments permeate the Petition, the Board should decline to institute IPR based on such a petition. Alternatively, the Board should strike Ariosa's *Prometheus* arguments and not consider them in deciding whether to institute IPR.

1. Ariosa has improperly based its Petition on Section 101.

Congress authorized a party filing a petition for inter partes review to “request to cancel as unpatentable [one] or more claims of a patent *only on a ground that could be raised under section 102 or 103 and only on the basis of prior art* consisting of patents or printed publications.” *See* 35 U.S.C. 311(b) (emphasis added). In contrast, Congress created the post-grant-review procedure to enable a petitioner to challenge patentability on “any ground.” *See* 35 U.S.C. § 321; *see also* 35 U.S.C. §282(b)(2) and (b)(3). Thus, IPRs may not be premised on challenges to whether a patent claims subject matter that is not eligible under Section 101.

Ariosa's Petition violates this fundamental principal that Section 101

challenges are not allowed in IPRs because the Petition asks the Board to make a determination of whether the '540 patent claims cover laws of nature within the meaning of Section 101. Though facially couched in the rubric of Section 102 and 103 analyses, Ariosa's reliance on *Prometheus* is a thinly-veiled attempt to have this Board decide Section 101 issues. Specifically, Ariosa urges this Board to use the following framework: (1) determine what claim limitations if any, are "associated with a law nature," (2) disregard those limitations, and (3) determine all Section 102 and 103 patentability issues considering only the remaining claim limitations. Petition at 30-32 (Ariosa argues: "[U]nder *Mayo v. Prometheus*, it is not appropriate to afford this aspect of the claim patentable weight."). Thus, Ariosa asks the Board to decide Section 101 issues—whether the patent claims cover patent-eligible subject matter. To do so in an IPR is prohibited by 35 U.S.C. §311(b).

2. Even if Ariosa is trying to limit the issues to Sections 102 and 103, *Prometheus* is not applicable.

Ariosa relies on legally-flawed arguments based on *Prometheus* to allege anticipation under Section 102 or obviousness under Section 103. *See e.g.*, Petition at 6:2-14. However, the Supreme Court's *Prometheus* holding does not apply to a Section 102 or 103 question. *See e.g., Prometheus*, 132 S. Ct. at 1304. To be sure, the *Prometheus* Court explicitly distinguished the Section 101 law of nature analysis from analyses under Sections 102, 103, and 112.

§§ 102 and 103 say nothing about treating laws of nature as if they were part of the prior art when applying those sections. . . .

See Prometheus, 132 S. Ct. at 1304 (emphasis added).

Since the Supreme Court issued its *Prometheus* decision, no federal court decision has applied *Prometheus* to a Section 102 anticipation or a Section 103 obviousness analysis, and Ariosa has therefore failed to identify any such decisions. And the Patent Office's interim procedure for a subject-matter-eligibility analysis does not suggest that *Prometheus* is applicable to any statutory section other than Section 101⁴. *See* 2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature. The interim guide specifically distinguishes *Prometheus*'s § 101 analysis from a §§ 102 and 103 analysis. *See id.* at p. 5. Additionally, the USPTO's post-KSR obviousness guideline does not mention *Prometheus* or laws of nature, further indicating that *Prometheus* is not relevant to an obviousness analysis. *See generally* Manual of Patent Examination Procedures § 2141.

Prometheus relates to a distinct requirement for patentability based on Section 101 that should not be comingled with an anticipation or obviousness

⁴ The Board should give the USPTO's guidelines on patentability at least instructive weight. *See e.g., Belkin Int'l Inc., v. Kappos*, 696 F.3d 1379 (Fed. Cir. 2012).

analysis under Section 102 or 103. Such a comingling is particularly improper in the context of an IPR, which must be based “only on a ground that could be raised under section 102 or 103 and only on the basis of prior art consisting of patents or printed publications.” Therefore, the Board should not institute IPR of the ‘540 patent. Alternatively, the Board should strike Ariosa’s Section 101-based arguments and not consider them in deciding whether to institute an IPR. All aspects of the claim must be considered in an anticipation or obviousness analysis. Section 102 requires that each and every element of the claim be present in the prior art, and Section 103 relates to whether “the subject matter as a whole” would have been obvious. 35 U.S.C. §§102 &103.

III. History of prenatal fetal nucleic acid detection

A. From the 1960s to the 2000s, researchers attempted to use rare fetal cells to effectively detect fetal nucleic acids—but failed.

In 1997, the accepted prenatal nucleic acid detection tests (chorionic villus sampling (CVS) and amniocentesis) were invasive and carried risk to the pregnant woman and her fetus. Ex. 1001 at 1:11-17.⁵ Because of the risk, the invasive procedures were only carried out on pregnancies in older women predisposed to aneuploidy, and thus only detected 30% of aneuploidies. 2006 at 218:1-¶2. Researchers had attempted to develop non-invasive—and thus lower-risk—

⁵ For additional technological background, see Ex. 1033 at ¶¶20-32.

diagnostic and screening techniques for decades⁶: “An old and so far unfulfilled dream ... is to have a method available which would allow *in utero* diagnosis of genetic anomalies without having to bear procedure-related risks to the mother and/or the fetus.” *Id.* at 218:1:¶1; Ex. 1011 at 848:1:¶2 to 849:2:¶2; Ex. 1024 at 2357:1:¶1 to 3:¶2. But such non-invasive methods did not involve amplifying and detecting fetal nucleic acids; they thus lacked sensitivity and carried a relatively high false-positive rate.⁷ Ex. 1025 at 1229:1:¶1; Ex. 1011 at 847:2:2. And those methods required a large number of women to undergo the risky, *invasive* DNA detection tests as a follow up to rule out false-positive results—a risk that some women chose not to take. Ex. 1011 at 847:1:¶2 to 848:1:¶1; Ex. 1033 at ¶¶ 36-37.

⁶ Such non-invasive methods were predictive for some aneuploidies (diseases caused by incorrect chromosome number), but were not predictive of other genetic diseases such as sickle cell anemia. Ex. 2007 at 264:1;¶¶1-2.

⁷ The non-invasive prior art screening methods did not *amplify or detect* fetal nucleic acid. They merely determined whether a fetus had an increased likelihood of having, e.g., Down syndrome (chromosome 21 trisomy) based on correlations with certain phenotypes. Ex. 2006 at 218:1:¶2; 2008 at 373:1:¶2. In contrast, the invention involves the specific detection of genetic abnormalities by amplifying and detecting paternally inherited fetal nucleic acid. Ex. 1033 at ¶ 33-37; Ex. 2008 at 373:1:¶¶1-2.

In 1969, researchers first recovered fetal cells from maternal blood and proposed that they might be used for non-invasive fetal DNA detection. Ex. 1024 at 2357:2; ¶2 to 3:¶1; Ex. 1025 at 1229:2:¶ 2.⁸ But in the 1980s and 1990s, researchers began to doubt whether nucleic acid from these cells could be the basis of such a method for at least three reasons: (i) fetal cells in maternal blood were rare, (ii) not all pregnant women had fetal cells in their blood, and (iii) some fetal cells persisted for decades after birth and were therefore unreliable for testing a subsequent pregnancy. Ex. 1024 at 1236:2:¶ 1 (“...all observers agree that fetal cells in maternal blood are rare.”) ; Ex. 1011 at 850:2:¶3 (“Fetal cells are extraordinarily rare in maternal blood.”) & 850:1:¶2 (“Also unknown is whether fetal cells are present in the circulation of all pregnant women.”); Ex. 2010 at 705:Title & Abstract (male fetal cells were found in maternal blood 27 years after birth).

Because there was such a need for non-invasive detection of fetal nucleic acid, researchers attempted many purification methods for these rare fetal cells. Ex. 1011 at 848:1:¶2 to 851:2:¶1. Specifically, researchers attempted to purify and detect DNA from fetal trophoblasts, fetal lymphocytes, fetal granulocytes, and fetal nucleated red blood cells. Id.; Ex. 1024 at 2357:2:¶2 to 2359:1:¶1; Ex. 1025 at

⁸ Scientists had known for more than a century that fetal cells were sometimes released into maternal blood. Ex. 2009 at 714:¶2.

1230:2:¶2 to 1233:1:¶3. But the rarity of these fetal cells and the inability to develop an adequate purification technique precluded researchers from successfully inventing a cell-based fetal nucleic acid detection method. Ex. 2011 at 35:2:¶¶2-3 (the very small number of fetal cells requires fetal cell enrichment but no antibodies had been developed to adequately carry out such enrichment); Ex. 2012 at 649:1:¶1 & 650:¶3 (a 2002 paper describing “sobering” preliminary results using fetal cells enriched using two different platform cell sorting technologies (FACS and MACS)—“neither approach can attain the degree of efficacy necessary for clinical application.”). So researchers abandoned this avenue. Ex. 1024 at 2357:3:¶1; Ex. 2013 at 10:2:¶1.

B. The ’540 patent’s invention revolutionized fetal nucleic acid detection.

Drs. Lo and Wainscoat’s invention set forth in the ’540 patent revolutionized non-invasive fetal diagnostics: “Finally, after years of hunting for the elusive fetal cells in maternal circulation ... , it seems that cell-free fetal DNA (cffDNA) will provide the basis for a safer, noninvasive approach to fetal diagnosis.” Ex. 2014 at 269:1:¶2.

Drs. Lo and Wainscoat were the first to suggest and demonstrate that the *non-cellular* portion of maternal blood contained fetal nucleic acid that could be amplified and detected for prenatal diagnosis and screening. Ex. 1001 at 1:50-67, 3:58-62 & 23:60 to 26:42 (claims); Ex. 1016 at 486; 2:¶2 (authored by Drs. Lo and

Wainscoat and colleagues). Dr. Daniels *et al.*, specialists in haemolytic diseases of the fetus and newborn, called their invention the “Holy Grail” of prenatal diagnosis. Ex. 2015 at 226:1:¶1 & 230:2:¶4. Dr. Uitto *et al.*, specialists in heritable diseases and prenatal diagnosis, exclaimed: “The recent demonstration that fetal DNA can be found in easily detectable quantities in maternal plasma has provided new possibilities for non-invasive prenatal testing.” Ex. 2016 at 341:2:¶3. Because of Drs. Lo and Wainscoat’s invention, and because of the decades-long failure by others to develop any other non-invasive fetal nucleic acid detection technique, the present invention is the basis for an entire new industry in fetal diagnostics. Ex. 2014 at 269:1:¶1 to 269:2:¶2; Ex. 2015 at Abstract; Ex. 2017 at 628:1:¶2; also see Section VIII. Moreover, Ariosa is attempting to enter the very field that Drs. Lo and Wainscoat pioneered.⁹

Despite the rare occurrence of fetal cells in maternal blood, cell-free fetal DNA is found in a surprisingly much higher concentration than might have been predicted: “Significantly more fetal DNA is present in the cell-free *plasma (or serum)* of pregnant women as compared with the fetal DNA extracted from the cellular fraction of maternal blood.” Ex. 2018 at S93:2:¶2 (emphasis in original)

⁹ Ariosa’s attempt to discredit the patentability of the ’540 patent’s claims is directly contradicted by Ariosa’s practice of that very method. Ex. 2020 at 319.e1, (authored by scientists at Ariosa Diagnostics, formerly Aria Diagnostics).

(“...surprisingly high mean concentrations of fetal DNA in maternal plasma DNA.”); Ex. 2019 at 195:2:¶1; Ex. 2015 at 226:1:¶4 to 226:2:¶1.¹⁰ Because of this unexpectedly high concentration, prenatal testing using this unexpected source of fetal DNA is sufficiently sensitive and accurate. Ex. 2021 at 864:2:¶1 (sensitivity and specificity “considerably higher than can be currently attained by the analysis of fetal cells.”); Ex. 2017 at 634:3:¶3 to 635:1:¶1. Plus, all pregnant women have cell-free fetal DNA in their blood, thus eliminating one of the concerns about fetal cells. Ex. 2008 at 373:1:¶2. And, unlike fetal cells that persist for decades after birth, cell-free fetal nucleic acid clears quickly from circulation. Ex. 2016 at 341:2:¶2.

Because of the pioneering work of Drs. Lo and Wainscoat, prenatal diagnosis now centers on noninvasive methods involving amplifying and detecting cell-free fetal nucleic acid rather than cellular nucleic acid. Ex. 2014 at 269:1:¶2;

¹⁰ Contrary to Ariosa’s theory on how fetal cell-free nucleic acid is released into maternal blood, death of circulating fetal cells cannot be the source of the extracellular DNA: “The origin of this fetal [cell-free] DNA is unknown.... [A]poptosis of these rare [fetal] cells alone cannot account for the quantity of fetal DNA in maternal blood.” 2015 at 226:2:¶1; 2021 at Abstract (no correlation exists between fetal erythroblast numbers and fetal cell-free DNA concentration in maternal circulation).

Ex. 2015 at Abstract; Ex. 2017 at 627:2-¶1: “Context” section. And their invention greatly reduces the percentage of women who need to undergo risky, invasive testing: “If referrals for amniocentesis or [CVS] were based on the sequencing test results [using the ‘540 patent’s claimed method], about 98% of the invasive diagnostic procedures could be avoided.” 2022 at 1:Abstract:Conclusion.

IV. Ariosa is not reasonably likely to prevail because it asserts references that are not prior art to the ‘540 patent.

Ariosa relies heavily upon references that cannot be considered prior art against the ‘540 patent, *viz.* Lancet 1997, Schallhammer, and Gocke. In an effort to introduce such alleged intervening art, Ariosa attacks the ‘540 patent’s entitlement to its priority date.¹¹ But this attack fails for at least three reasons: (i) the ‘540 patent’s March 4, 1997 priority application fully enabled and adequately described the ‘540 patent claims, (ii) Ariosa failed to introduce any evidence—and thus failed to meet its burden—to establish the effective dates of Lancet 1997,

¹¹ Ariosa must prevail in its priority attack to assert that Lancet 1997, Schallhammer, and Gocke are prior art. Ariosa relies on these references as essential components of the following grounds of alleged unpatentability: Grounds A (anticipation over Lancet 1997), B (obviousness over Lancet 1997 and Simpson 1994), D (obviousness over Simpson 1994, Schallhammer, and Kazakov), and E (obviousness over Gocke, Robbins, and Simpson 1994).

Schallhammer and Gocke, and (ii) at least Lancet 1997 can be sworn behind or can be removed under *In re Katz*.

A. The '540 patent is entitled to its earliest priority date of March 4, 1997, eliminating several of Ariosa's references.

The '540 patent is entitled to its earliest filing date of March 4, 1997, thus eliminating Lancet 1997, Schallhammer, and Gocke as prior art.¹² To assert intervening art against the '540 patent, Ariosa argues that the patent is not entitled to the filing date of its priority application, alleging (i) embodiments of the '540 patent claim that require *a priori* testing or precise quantitation were not enabled on the priority application's filing date, and (ii) the priority application did not adequately describe the claim term "fetal." Petition at 22-29. But the '540 patent's priority application fully enabled and adequately described the '540 patent's claims. Therefore, three of Ariosa's asserted references are not prior art.

1. The priority application fully enabled the '540 patent claims in view of the state of the art.

In challenging enablement, Ariosa argues (i) that for many prenatal diagnostic methods, it was necessary to know the maternal and paternal alleles before DNA detection ("*a priori*" testing), which Ariosa contends would have been "burdensome," and (ii) even with *a priori* testing, quantitative PCR techniques

¹² Ariosa cannot prevail on any of its grounds A, B, D, or E if Lancet 1997, Schallhammer, and Gocke are not prior art.

were not sensitive enough to detect fetal aneuploidies until at least 1999. Petition, at 14-16 & 23-25.

Ariosa's enablement challenge must fail. It is premised on a legally flawed analysis and its factual premises are false—*a priori* genotype testing and digital PCR, a sufficiently sensitive PCR technique, were readily available before the filing date of the priority application.

(a) Ariosa's enablement attack relies on a legally flawed analysis.

In attacking enablement of the '540 patent, Ariosa relies upon a legally-incorrect standard. Ariosa argues the '540 patent's priority application does not enable the claims because it would have been "burdensome" to obtain *a priori* knowledge of the maternal and paternal alleles. Petition at sentence bridging 24-25. But the enablement requirement is met even where a component is burdensome. It is *not* met only if undue experimentation would have been needed. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Ariosa does not argue or introduce evidence that *any* experimentation, let alone undue experimentation, would have been necessary to obtain *a priori* knowledge of maternal and paternal alleles.¹³ Ariosa's failure to

¹³ No evidence supports many of Ariosa's contentions. Specific to enablement, Ariosa's Petition at page 23 cites the Kazakov and Vasioukhin declarations but the cited paragraphs of the declarations do not cite any supporting

show that *undue experimentation* would have been necessary means that Ariosa has not met its burden to establish lack of enablement.

(b) Methods to obtain *a priori* knowledge of maternal and paternal alleles were readily available.

Even if Ariosa's enablement attack were not legally flawed, its argument fails on the facts: Ariosa's witness, Dr. Barker, admits that *a priori* methods were readily available:

... paternally-inherited sequences that are different in the father and mother are easily detectable using sequence-specific primers that do not amplify maternally-derived DNA (i.e., allele-specific primer targeting the paternal allele) and standard or qPCR methods, all of which were well-known and widely used at the time of the filing of the '540 priority document.

Ex. 1005 at ¶24. And before the priority date, more than 15,000 human STS genomic markers were publicly available for carrying out genotyping; researchers had mapped and published these STS markers in 1995. *See* Ex. 2023 at ¶1. There is no dispute that methods for obtaining *a priori* knowledge were readily available at the time the priority application was filed.

evidence. Ex. 1006 at ¶¶64-69; Ex. 1008 at ¶¶31-35. Fed. R. Evid. 705; § 42.65; *Rohm & Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997) (the Federal Rules of Evidence and Federal Circuit jurisprudence do not require the fact finder to give weight to an expert witness's unsupported assertions).

(c) Sufficiently precise quantitative analysis techniques were readily available before the filing date of the priority application.

Ariosa asserts that the priority application, filed March 4, 1997, did not enable the '540 patent's claims because "precise quantitative analysis such as digital PCR" was not available, but Ariosa is wrong.¹⁴ Petition at 25.¹⁵ Digital PCR (dPCR) was available before the filing date of the priority application, and Ariosa does not contend that dPCR would not have been a sufficiently precise method to practice the '540 patent's claims. Ariosa's expert Barker concedes that dPCR was

¹⁴ Ariosa's "Technical Background" section states that next generation sequencing was required. Petition at 16-18. But Ariosa later admits that *either* next generation sequencing *or digital PCR* would have enabled the invention. Petition at 25. Ariosa's experts also admit that digital PCR would have enabled the invention. Ex. 1005 at ¶¶ 12-13; Ex. 1007 at ¶ 32.

¹⁵ Ariosa's expert Mansfield opined that quantitative detection of aneuploidies would not have been possible when the priority application was filed (March 4, 1997). Ex. 1007 at ¶ 26. But her opinion is contradicted by her own patent no. US 5,994,057 and publication. Ex. 2024; Ex. 1018. The publication describes, and the '057 patent describes and claims, "the detection of aneuploidy by the quantitative amplification of selected short tandem repeat (STR) DNA." Ex. 2024 at 2:11-13& 13:1 to 14:40 (claims); Ex. 1018 at 43:Title & Abstract.

available: “Techniques that allow for single molecule counting were not available (next generation sequencing) or not capable of the highly-parallel reactions and detection necessary (dPCR) at the time of the filing of the ’540 priority document.”¹⁶ Ex. 1005 at ¶ 25.

Although artisans had not yet coined the term “digital PCR,” the digital PCR method had been published by no fewer than three research groups well before 1997. *See, e.g.*, Ex. 2025; Ex. 2026; Ex. 2027; Ex. 2028; *see also* Ex. 2029 at 8604:1:¶2; Ex. 2030 at 10:2:Future Perspective:¶2 (each citing Ex. 2027 as the first publication of digital PCR). Ignoring such readily-available evidence, Ariosa’s experts contend that dPCR was not available until 1999 or 2006. Ex. 1005 at ¶12 (citing Vogelstein 1999 (Ex. 2031)); Ex. 1007 at ¶33 (citing Quake U.S. patent no. 7,888,017, with an alleged priority date in 2006).

Ariosa’s experts are wrong: substantively, each of Simmonds, Sykes, Brisco and Levinson independently discloses Vogelstein 1999’s dPCR method. As Ariosa’s expert Barker explains:

¹⁶ Ariosa does not contend that “highly-parallel reactions and detection” were needed to enable the claims. And it is too late for Ariosa to make this contention. In any event, even if such features were desirable for commercialization, they were not needed for enablement, of the claimed method.

With dPCR, the nucleic acid sample is partitioned so that individual nucleic acid molecules within the sample are localized in separate small volumes ... typically in *a dilution of only one molecule in every two chambers*. As a result, each small volume will contain one or no molecules, resulting in a *positive or negative PCR reaction*, respectively. The separation of the nucleic acids *allows for counting of individual molecules*, resulting in a more reliable and sensitive measurement of nucleic acids than can be obtained by standard PCR or by qPCR, as *low copy number sequences are not “swamped out”* by high copy number sequences, and amplification bias is effectively eliminated.... [Then the amplified] nucleic acids are *quantified* by counting the number of locations that contain a PCR end-product; for example, by using differently-labeled oligonucleotide probes as was typical before the development of next-generation sequencing techniques.

Ex. 1005 at ¶ 12 (emphases added). Another essential feature according to Vogelstein 1999 is that: “Significance can be established through rigorous statistical analysis as positive signals should be distributed according to Poisson probabilities.” Ex. 2031 at 9239:2:¶3. Each pre-1997 publication discloses these characteristics. Ex. 2025 at 865:1:¶2 & 867:1:¶¶2-4; Ex. 2026 at 215:1:¶3 to 215:2:¶2; Ex. 2027 at 444:1:¶¶1-2 & 444:3:¶1; Ex. 2028 at 318:2:¶3 & 321:1:¶¶2-3. So Ariosa is mistaken—the claims were fully enabled as of March 4, 1997.

Ignoring these facts, Ariosa incorrectly asserts that Dr. Lo, an inventor of the ’540 patent, admitted in a 2011 article that the quantitative methods necessary for

the '540 patent's claims were not available until the mid-2000's. Petition at 17-18 & 25-26. But Dr. Lo's publication merely mentioned papers by others reporting on the *demonstrated* use of the claimed invention; he did *not* state that the claimed invention *could* not have been performed at an earlier date. And Dr. Lo is an academician who describes research in the conservative manner that is common among academicians. These statements are not admissions.

Because genotyping and digital PCR methods were both enabled by the art as of March 4, 1997, the priority application fully enabled the '540 patent claims. Ariosa cannot prevail in seeking to introduce intervening art.¹⁷

¹⁷ Ariosa also incorrectly contends that quantitative PCR methods available in March 1997, other than digital PCR, were not sufficiently precise to enable the invention. But Ariosa's contention is based on incorrect factual assertions and thus is wrong. In fact, contrary to Ariosa's contention, Heid—cited in the '540 patent as an exemplary quantitative method—taught the real time PCR method, which would have been precise enough to enable the claims. Ex. 1001, e.g., at 3:49-51.

Because Ariosa has admitted that digital PCR was sufficiently precise, and because Isis has shown above that digital PCR was available in March 1997, this Preliminary Response need not address Ariosa's contention about other prior art quantitative PCR methods. Nonetheless, some of Ariosa's incorrect factual assertions are noted. First, Mansfield cites to Wilkenson 1995 as being the

2. The priority application adequately described the claims—the '540 patent specification did not change the scope of the term “fetal.”

Ariosa also challenges the '540 patent's priority date by arguing that the priority application did not adequately describe the '540 patent's claims, which are directed to *fetal* testing. Petition at 27-29. Ariosa specifically asserts that the '540

quantitative PCR method used in the '540 patent, but the '540 patent cited Heid, not Wilkenson. Ex. 1007 at ¶24; Ex. 1001 at 3:51, 6:37, 8:14, 10:17, etc. Second, Wilkenson describes competitive PCR, not Heid's real time PCR method. Ex. 2032 at 363:Title & Abstract; Ex. 2033 at 991:2:¶¶3-4. Third, Mansfield discusses standard error, but the correct value to use when comparing the accuracy of different methods is the coefficient of variation (CV). Ex. 1007 at ¶¶24, 28 & 36; Ex. 2034 at 44:Section 1.16 (especially ¶1 of that section). Wilkenson disclosed that his PCR method introduced a CV of 12%, whereas Heid's method had a CV of only 0.90-0.94%. Ex. 2032 at 365:3:¶4; Ex. 2033 at 990:Table 1. Thus, Heid's method (cited in the '540 patent) is significantly more precise than Wilkenson's (relied upon by Mansfield). Fourth, researchers knew they could increase the precision of quantitative PCR methods by increasing the number of replicate reactions, but Ariosa's experts ignore this basic technique for increasing precision of the claimed method. For at least these reasons, Ariosa fails to establish that the '540 patent did not disclose a sufficiently precise quantitation method.

patent enlarged the scope of the term “fetal” to include gestational weeks 7 to 40 when it changed the following paragraph of the specification:

It is anticipated that it will be possible to incorporate the nucleic acid-based diagnosis methods described herein into existing prenatal screening programmes. Sex determination has successfully been performed on pregnancies from 7 [12] to 40 weeks of gestation.

Ex. 1001 at 3:58-62; Ex. 1004 at 6:3-6 (the differences between the two specifications are indicated).

Ariosa’s argument misses the mark. The changed portion of the specification does not even refer to “fetal,” let alone broaden the scope of a definition of fetal.¹⁸ In fact, the quoted passage broadly discloses the successful use of the invention in “*prenatal* screening programmes.” “Prenatal” covers the entire period from conception to birth.

Although this amendment of the specification had nothing to do with the scope of “fetal,” Ariosa nevertheless attempts to support its argument by citing a *pathology* textbook that defines “embryonic” as weeks 0 to 9 of gestation and “fetal” as gestation week 10 through birth. Petition at 28 (citing Ex. 1020). But *pathology* is not the relevant art. In the relevant field of prenatal diagnosis, the

¹⁸ Ariosa is incorrect when it discusses a definition of “fetal” in the relevant specification; there is no such definition in either specification.

term “fetal” is generic to both “fetal” and “embryonic.” For example, Bianchi describes a study of “fetal” cells at gestation week 7 (and 26) and Simpson refers to male “fetuses” at gestation days 33-40 and refers to “fetal” cells at gestation week 6. Ex. 1011 at 850:1:¶1; Ex. 1025 at 1236:2:¶2. According to Ariosa’s pathology text, these pre-gestation week 10 fetuses and fetal cells should be called embryos and embryonic cells. But prior to March 4, 1997 and now, the non-invasive prenatal diagnosis field—as opposed to the pathology field—includes embryonic and fetal under the umbrella of “fetal.” Ex. 2017 at 633:1:¶2 (a 2011 publication describing “no fetal DNA amplification” in gestation week 7 samples) & 634:3:¶3 to 634:1:¶1.

Ariosa also relies on *Chiron*, but that case is inapposite. *Chiron Corp. v. Genentech, Inc.*, 363 F. 3d 1247, 1258 (Fed. Cir. 2004). In *Chiron*, the patent explicitly defined the term at issue: “the term ‘monoclonal antibody’ refers to” *Id.* Here, there is no definition in the patent for “fetal.” And the *Chiron* court never reached the issue of whether the patent introduced new matter by expanding the scope of the term: “... the record amply supports the jury’s verdict of invalidity *without reaching this complex claim construction question.* *Chiron* at 1258 (emphasis added). Thus, *Chiron* does not support Ariosa’s arguments.

For these reasons, Ariosa cannot prevail in attacking the priority date for the ’540 patent. As explained above, because Isis is entitled to its priority date and

Ariosa failed to establish earlier effective dates for Lancet 1997, Schallhammer, and Gocke, these references are not prior art. Thus, Ariosa cannot prevail on its unpatentability grounds A, B, D, or E.

B. Ariosa did not introduce evidence to meet its burden to show when the asserted references became available to the public under Section 102(a) or effective under Section 102(e).

Even if Ariosa is successful in attacking the priority date of the '540 patent, Ariosa had the burden to establish that all of its cited references are prior art, but Ariosa failed to introduce such evidence for three asserted references. A challenger of patentability has the initial burden of presenting sufficient evidence to establish an earlier effective date for alleged prior art that the challenger relies on in its grounds for instituting *inter partes* review. *See, e.g., Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) (patent challenger bears the initial burden on all issues relating to the status of alleged prior art, including effective dates). Ariosa had the burden to establish that all of its cited references are prior art, but Ariosa failed to meet that burden.

1. Lancet 1997 is not prior art or can be removed as prior art.

Ariosa calls Lancet 1997 “intervening” art.¹⁹ Petition at 34:¶1. On its face, Lance 1997 was published in August 1997, after the '540 patent’s priority date of

¹⁹ Lancet 1997 was asserted under Ariosa’s grounds A and B. It was co-authored by Drs. Lo and Wainscoat and their colleagues.

March 4, 1997. Ex. 1016 at 485:bottom left margin. Because the '540 patent is entitled to its priority date for the reasons discussed above, Lancet 1997 is not prior art to the '540 patent.

But even if the '540 patent is not entitled to its priority date, Isis will remove Lancet 1997 under *In re Katz*. *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Ariosa alleges that Noemi Corbetta—a former laboratory technician named as an author on Lancet 1997—contributed to the invention's conception. Petition at 35-38. Ariosa thus attempts to cast doubt on whether Lancet 1997 can be disqualified under *In re Katz*.

Ariosa's suggestion that Ms. Corbetta may be a co-inventor is remarkable for its lack of evidentiary support. No evidence of record establishes that Ms. Corbetta made an *inventive* contribution to the claimed method or that she even contends to have made an inventive contribution. And whether any experimental methods were designed by Ms. Corbetta, as asserted by Ariosa, simply is not probative of conception of the invention. Thus, Ariosa's attempt does not rise to the level that would require Drs. Lo and Wainscoat to adduce any evidence beyond *Katz's* requirements. *Ex parte Kroger*, 219 USPQ 370, 1982 Pat. App. Lexis 3, at *4 (B.P.A.I. Nov. 22, 1982) (*Katz* declaration not sufficient given submission to USPTO of unnamed co-author's letter declaring himself to be a co-inventor and his refusal to sign a declaration stating that he was not a co-inventor). Thus, if needed,

Isis will remove Lancet 1997 under *In re Katz*. Alternatively, Drs. Lo and Wainscoat will swear behind Lancet 1997.

For any one of these reasons, Lancet 1997 is not prior art, and Ariosa cannot prevail on its unpatentability grounds A or B.

2. Schallhammer is not prior art or can be removed.

Ariosa bears the burden of producing sufficient evidence that Schallhammer was made accessible to the public under 35 U.S.C. § 102(a) prior to Isis Innovation's priority date.²⁰ *See Carella v. Starlight Archery and Pro Line Co.*, 804 F. 2d 135, 139 (Fed. Cir. 1986). Ariosa did not attempt to establish the publication date of Schallhammer beyond asserting that it was published in 1997. But, in fact, Schallhammer was published in a quarterly journal in *July* 1997, after the '540 patent's priority date. The public first received Schallhammer on July 28, 1997. Ex. 2035 at first page of exhibit (with a date stamp receipt of 7/28/1997); *see also In re Bayer*, 568 F. 2d 1357 (CCPA 1978); *In re Lister*, 583 F.3d 1307, 137 (Fed. Cir. 2009); and *In re Schlittler*, 234 F.2d 882, 110 USPQ 304 (CCPA 1956). Because Schallhammer was published after Isis Innovation's priority date and because the '540 patent is entitled to its priority date, Schallhammer is not prior art. Drs. Lo and Wainscoat will also be able to swear behind Schallhammer, if

²⁰ Schallhammer 1997 was asserted under Ariosa's unpatentability ground D.

needed.

For either of these reasons, Schallhammer cannot be prior art, and Ariosa cannot prevail on its unpatentability ground D.

3. Ariosa failed to establish that Gocke's effective filing date is before the '540 patent's priority date.

Ariosa did not carry its burden to establish that Gocke's effective date under Section 102(e) is earlier than Gocke's most recent filing date.²¹ *Mahurkar*, 79 F.3d at 1576. Since the filing date (March 14, 1997) of the application that issued as Gocke is later than the earliest filing date (March 4, 1997) of the '540 patent, at least one of Gocke's priority applications would need to provide support for the disclosure Ariosa relies upon in its unpatentability ground for Gocke to qualify as prior art. *In re Giacomini*, 612 F.3d 1380, 1383 (Fed. Cir. 2010). Ariosa has failed to establish that such a requirement has been met. Because Gocke states it is a continuation-in-part and thus added new matter, Ariosa's failure to show that any of its earlier applications included the critical disclosure is a fatal shortcoming.

Gocke states that it "is a continuation-in-part of U.S. Provisional Application, Serial No. 60/028,180, filed Oct. 15, 1996, which is a continuation-in-part of U.S. Provisional Application, Serial No. 60/026,252, filed Sep. 17, 1996, which is a continuation-in-part of U.S. Provisional Application, Serial No.

²¹ Gocke was asserted under Ariosa's unpatentability ground E.

60/013,497, filed Mar. 15, 1996.” Gocke (Ex. 1002) at 1:6-11. Thus, Gocke included additional disclosure at each filing date. Ariosa had the burden to establish that one or more of Gocke’s earlier applications included the disclosures on which Ariosa has relied. Ariosa failed to meet this burden.

Thus, Gocke cannot be prior art, and Ariosa cannot prevail on its unpatentability ground E.

V. Ariosa is not reasonably likely to prevail because its claim interpretation is unreasonably broad—it eliminates an entire recited step.

Ariosa cannot prevail because its claim construction is unreasonably broad—eliminating an entire step.²² The Board’s rules state that “[a] claim in an unexpired patent shall be given its broadest *reasonable* construction in light of the specification of the patent in which it appears.” 37 C.F.R. §§42.100(b) (2012) (emphasis added); *see also In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010) (stating that claim language should be read in light of the specification and teachings in the underlying patent); and Office Patent Trial Practice Guide, 77 Fed. Reg. 48764 (Aug. 14, 2012) (stating that the Board will construe claims “consistent with the Office’s practice in other proceedings.”).

Here, Ariosa ignores that claim 1 includes two distinct steps:

²² Under a correct claim construction, Ariosa cannot prevail on its unpatentability grounds C-E.

1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises

amplifying a paternally inherited nucleic acid from the serum or plasma sample and

detecting the presence of a *paternally inherited nucleic acid of fetal origin* in the sample.

Ariosa ignores the second step, asserting: “[T]he term ‘detect’ does not require identification of a nucleic acid as paternally inherited.” Petition at 19:¶ 2. This construction decouples the verb “detect” from its direct object—paternally-inherited nucleic acid of fetal origin. In decoupling the verb “detect” from its object, Ariosa renders the term “detect” meaningless and gives no weight to a material limitation—the entire second step of the claim. This is *not* the broadest *reasonable* construction.

And Ariosa misstates licensee Sequenom’s preliminary claim construction in a related litigation when Ariosa states: “to ‘detect’ a nucleic acid means to discover or determine its existence or presence, *without regard to identification of its origin*.” Petition at 19:block text (emphasis added) (citing Ex. 1031 at 8:4 to 9:5). Sequenom did not include such “without regard” language in its construction. Ex. 1031 at 8:19-23. Rather, Sequenom’s Motion for Preliminary Injunction actually says: “to ‘detect’ a nucleic acid means to discover or determine the existence, presence, or fact of it.” Ex. 1031 at 8:21-23. In that litigation, Sequenom simply

construed “detecting” separately from the phrase “the presence of a paternally inherited nucleic acid of fetal origin in the sample.” Ex. 1031 at 8:19-23. But Sequenom gave weight to *both* terms, contrary to Ariosa’s contention in this IPR:

The person of ordinary skill in the art would understand “detecting the presence of” to have its ordinary and customary meaning and does not need to be construed. If a construction is required, the person of ordinary skill in the art would understand this phrase to mean “discovering or determining the existence, presence, or fact of.” They would also understand “paternally inherited nucleic acid of fetal origin” to mean “a nucleic acid that originated from the fetus and which was inherited from the father.”

Ex. 1033 at ¶ 104.

Ariosa’s quotation of and citation to the Evans declaration also fails to support its position. Petition at 20: block text. Specifically, Ariosa cites Ex. 1033 at ¶108:23-26, but this section discusses Ariosa’s infringing method; it does not discuss claim construction. Ariosa also cites Ex. 1033 at ¶ 98, but this paragraph discusses “amplifying,” not “detecting.”

Under the broadest *reasonable* construction, claim 1’s terms have their ordinary and customary meanings:

“A method of detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises”

“amplifying a paternally inherited nucleic acid from the serum or plasma sample”

“detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.”

Notably, under the broadest reasonable construction, the “amplifying” and “detecting” steps are distinct, contrary to Ariosa’s construction.

Focusing on the “detecting” step, its ordinary and customary meaning is consistent with the ’540 patent’s specification: it requires distinguishing, at some point, fetal from maternal DNA. In the specification’s example 1, a Y-specific sequence is amplified and then detected: “PCR products were analyzed by agarose gel electrophoresis and ethidium bromide staining.” Ex. 1001 5:23-24. In this example, because the primers were Y-specific, detection of the PCR product was detection of “the presence of a paternally inherited nucleic acid of fetal origin” in the sample. The ’540 patent also describes other detection methods such as linkage analysis and “quantitation of fetal DNA markers on different chromosomes” to detect aneuploidy. Ex. 1001 at 3:11-24 and 3:44-51.

But Ariosa’s construction—leaving out the material “detecting” limitation—is so broad that it cannot stand. Under a broadest reasonable construction, Ariosa cannot prevail on its unpatentability grounds C-E.

VI. Ariosa does not have a reasonable likelihood of prevailing on any of its proposed unpatentability grounds.

When the claims are given their broadest reasonable interpretation, Ariosa

does not have a reasonable likelihood of prevailing on any of its proposed unpatentability grounds for at least these reasons: (i) Ariosa failed to establish that several references are prior art, (ii) Kazakov 1995 is missing at least one material limitation, (iii) Ariosa failed as a matter of law to establish that Kazakov inherently anticipates the claims, (iv) Ariosa failed as a matter of law to establish *prima facie* obviousness (a) by not showing a reason to combine the references and (b) by not showing a reasonable expectation of success.

Isis addresses each of Ariosa's grounds A-E individually. Petition at 37-57. The discussion will focus on independent claim 1 because claims 2-27 are narrower than claim 1 and because, without a reasonable likelihood of prevailing on the broadest independent claim, there cannot be a reasonable likelihood of prevailing on the narrower claims. *E.g., In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992) ([D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious.")

A. Ariosa's unpatentability ground A—claims 1-2, 4-5, 19-22, and 24-25 are anticipated by Lancet 1997—does not have a reasonable likelihood of prevailing.

Ariosa is unlikely to prevail on its unpatentability ground A for two reasons: (i) Lancet 1997 is not prior art to the '540 patent, as is discussed above, and (ii) even if the '540 patent is not entitled to its priority date, Lancet 1997 can be disqualified as prior art, as is discussed above. So Ariosa cannot prevail on this

ground of unpatentability.

B. Ariosa's unpatentability ground B—claim 8 is obvious over Lancet 1997 in view of Simpson 1994—does not have a reasonable likelihood of prevailing.

Ariosa is unlikely to prevail on its ground B because, as is discussed above, Lancet 1997 is not prior art or it can be removed. Ariosa did not argue in the alternative that Simpson 1994 alone renders obvious claim 8. Petition at 42. But, if Ariosa had made this argument, the evidence below regarding Ariosa's unpatentability grounds D and E shows that Ariosa could not have prevailed based on Simpson 1994 alone.

C. Ariosa's unpatentability ground C—claims 1-2, 4-5, 8, 19-22, 24-25 are inherently anticipated by Kazakov—does not have a reasonable likelihood of prevailing.

Ariosa is unlikely to prevail on its position that Kazakov inherently anticipated claims 1-2, 4-5, 8, 19-22, and 24-25 because Kazakov failed to disclose, expressly or inherently, at least one material limitation.

1. Kazakov does not disclose, either expressly or inherently, the recited detection step.

Ariosa admits that Kazakov did not disclose claim 1's step 2—detection of paternally inherited DNA of fetal origin: “[T]he Kazakov process did not ... identify the extracellular DNA as specifically fetal, or distinguish paternally-inherited fetal DNA from maternally-inherited fetal DNA.” Petition at 45:2-¶5; Ex. 1006 at ¶21 (Ex. 1006 is a declaration by the first author of Kazakov). As Kazakov

did not expressly teach claim 1's detection step, Ariosa once again ignores this step. Thus, Ariosa's proposed ground of unpatentability must fail.

2. Ariosa fails to prove that Kazakov inherently discloses the recited amplification step.

Because Kazakov does not teach the detection step, Ariosa instead attempts to prove that Kazakov necessarily performed the *amplification* step—i.e., that Kazakov amplified a paternally inherited nucleic acid (on the Y chromosome) from maternal serum or plasma. But, for at least two reasons, Ariosa's evidence fails to show even this: (a) as a matter of law, Ariosa failed to prove that Kazakov inherently discloses this limitation, and (b) for scientific and legal reasons, Ariosa's evidence failed to prove what Ariosa alleges it does.

(a) Ariosa's alleged proof of inherency fails as a matter of law.

Ariosa failed as a matter of law to prove that Kazakov inherently discloses even the *amplification* step. A reference inherently discloses a claim limitation if it is the "natural result" flowing from the explicit disclosure of the prior art. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). But "[i]nherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient." *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F. 2d 1264, 1269 (Fed. Cir. 1991) (citations omitted) (emphasis added).

And, in determining whether a limitation is inherent, *it is improper to conjecture* as to what a reference would teach *if* it were carried out in a manner not expressly disclosed. *Perricone v. Medicis Pharmaceutical Corp.*, 432 F. 3d 1368, 1378 (Fed. Cir. 2005). In *Perricone*, one claim at issue was directed to a “method for treating skin sunburn by topically applying to the skin sunburn” a particular lotion. *Id.* A prior art reference expressly disclosed the recited lotion and its topical application to skin. *Id.* at 1376. In reversing the district court’s holding that the reference inherently anticipated the claim, the Federal Circuit reasoned that the lower court had merely conjectured: “*The issue is not ... whether [the prior art’s] lotion **if** applied to skin sunburn* would inherently treat that damage, but whether [the prior art] discloses the application of its composition to skin sunburn. It does not....” *Perricone* at 1378 (bold and italic emphases added).

Here, Ariosa attempts to show that *if* Kazakov had performed amplification using the Tc65 primer on maternal serum samples containing *male* fetal DNA, he would have amplified paternally inherited fetal nucleic acid. But Kazakov is silent as to the gender of the fetuses. Ex. 1014. And Ariosa provided no evidence that Kazakov’s maternal samples contained DNA from male fetuses. Petition at 44-45; Ex. 1006 at ¶¶11 & 26; Ex. 1007 at ¶¶51-69. Nor did Ariosa’s expert Mansfield carry out the Kazakov experiment on Kazakov’s original samples. Ex. 1006 at ¶¶52 & 55. So Ariosa’s experts merely speculate as to what Kazakov would have

inherently disclosed *if* it had applied its method to male fetal DNA. “Y chromosome sequences ... must have been amplified ... if the fetus was of a male gender.” Ex. 1006 at ¶26 (cited by Petition at 44).²³ But this is improper. *Perricone*, 432 F. 3d at 1378. And because all of Kazakov’s samples could have contained nucleic acid from female fetuses and no male fetuses, *Ariosa failed as a matter of law* to prove that Kazakov inherently amplified Y chromosome nucleic acid. Thus, Kazakov is missing *both* the amplifying and the detecting steps of claim 1.

(b) Ariosa’s evidence fails to prove inherency because it is factually and legally flawed.

Ariosa’s evidence is factually and legally flawed and thus fails to prove that Kazakov inherently amplified cell-free fetal nucleic acid. First, Kazakov itself provides evidence that cell-free fetal DNA was not amplified. Kazakov amplified sequences using the Tc65 primer in first trimester samples but *not* in third trimester

²³ Ariosa’s Petition at 44 cites the Kazakov declaration (Ex. 1006), paragraphs 11 and 26, as supporting that primers C and D used in Kazakov amplified Y chromosome sequences. But the only support the Kazakov declaration cites are exhibits 48-49 (alleged Blast searches)—and neither the resubmitted version of his declaration nor the original version of his declaration includes exhibits 48-49. For this additional reason, Ariosa’s argument must fail.

samples. Ex. 1014 at 234:¶3. Yet the concentration of cell-free fetal DNA *increases* in the third trimester. Ex. 1001 at 1:59-62; Ex. 2016 at 341:2:¶3 (“[cell] free fetal DNA ... progressively increases during pregnancy...”). So if Kazakov’s Tc65 primer had actually amplified fetal DNA, then Kazakov should also have seen amplification products from the third-trimester maternal samples. But he did not. Thus, Kazakov itself provides evidence to doubt Ariosa’s inherency theory.

Second, because of Mansfield’s experimental design, Ariosa’s evidence is legally and factually insufficient to prove what Kazakov allegedly inherently discloses. Kazakov was interested in the mechanisms leading to increased cell-free DNA in the blood of pregnant women and the possible regulatory role of such DNA. Ex. 1014 at 234:¶2 to 235:¶1. The authors used PCR to test the DNA for inter-Alu sequences using primer Tc65 and analyzed the PCR products by gel electrophoresis that did not discriminate any individual PCR products. *Id.* at 234:¶3 & Inset VIII:Fig. 2 (showing a smear of amplified fragments varying greatly in size). Ariosa thus cannot point to Kazakov to show that the Tc65 primer amplified paternally inherited fetal DNA—it is impossible to detect any particular PCR fragment, much less a Y-specific one: “The fact that total human DNA amplifies as a smear suggests that sufficient numbers of fragments are amplified to obscure individual sequences.” Ex. 2036 at 6687:2:¶2 & 6688:Fig. 2(A), lane 2. Nelson was Kazakov’s source for the Tc65 primer sequence. Ex. 1014 at 233:¶5. And

Nelson had shown only that Tc65 amplifies a sequence on the X chromosome. Ex. 2036 at 6687:2:¶4 to 6688:1:¶1. Nelson is silent about whether Tc65 amplifies Y chromosome sequences. Ex. 2036 at 6687:1:Table 1 (showing that none of the somatic cells hybrids that Nelson tested contained any part of chromosome Y).

In an attempt to fill in what Kazakov and Nelson do not expressly (or inherently) disclose, Ariosa's expert Mansfield allegedly repeated Kazakov's experiment to prove that Tc65 amplifies a Y chromosome sequence (when used alone, Tc65 amplifies inter-Alu sequences). Ex. 1007 at ¶46. But, significantly, Mansfield did not use the same PCR conditions as Kazakov. For example, Kazakov used 2-5 mM Mg^{2+} , while Mansfield used 5 mM Mg^{2+} . Ex. 1014 at 233:¶5; Ex. 1007 at ¶57. This difference is highly likely to have affected the outcome of the experiment: "[T]he spectrum of fragments obtained in Alu-PCR [such as when Tc65 is used] depends to a very large extent on the conditions of PCR, especially on the concentration of Mg^{++} ." Ex. 2037 at 511:Fig. 1 (showing Tc65) & 514:¶4. Thus, although Mansfield purported to have amplified a Y chromosome sequence in her experiment, this alleged evidence is scientifically flawed and cannot be given any weight to prove that Kazakov also amplified this sequence. For Mansfield's experiment at best showed that Kazakov *might* have amplified Y chromosome DNA—if his samples even contained male fetal DNA; it did not prove that amplifying Y chromosome DNA was a *necessary* result of

Kazakov's experiment. As such, Ariosa's evidence is also legally insufficient to prove inherency. *Continental Can Co.*, 948 F. 2d 1264, 1269.

Because Kazakov did not expressly disclose the "detecting" step, and because Ariosa failed legally and scientifically to prove that Kazakov inherently carried out even the "amplifying" step, Ariosa cannot prevail on its unpatentability ground C.

D. Ariosa's unpatentability ground D—claims 1-2, 4, 8, 21-22, and 24-25 are obvious over Simpson 1994 in view of Schallhammer and Kazakov—does not have a reasonable likelihood of prevailing.

Ariosa does not have a reasonable likelihood of prevailing on its unpatentability ground D for at least four reasons: (i) Schallhammer is not prior art or can be removed as prior art; (ii) Ariosa failed as a matter of law to establish *prima facie* obviousness, (iii) there was no reasonable expectation of successfully carrying out the invention, and (iv) Simpson 1994 and the prenatal diagnosis art as a whole taught away from the combination with Kazakov.

First, Ariosa is not likely to prevail on this ground because Schallhammer is not prior art—either the '540 patent is entitled to its priority date of March 4, 1997, before Schallhammer's publication date, or Drs. Lo and Wainscoat will swear behind Schallhammer.

Second, Ariosa failed to prove its *prima facie* case based on these references as a matter of law. A *prima facie* case of obviousness requires evidence that a

person of ordinary skill in the art had a reasonable expectation of success in carrying out the invention. *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). Ariosa failed even to address this requirement, much less provide any evidence sufficient to establish *prima facie* obviousness. Thus, Ariosa has not established that it is reasonably likely to prevail.

Third, a person of ordinary skill in the art of noninvasive fetal nucleic acid detection would not have had a reasonable expectation of amplifying and detecting paternally inherited cell-free fetal DNA in maternal blood without the benefit of knowledge of the '540 patent's invention. Specifically, under Ariosa's theory that researchers expected most cells to release DNA into circulation, a researcher would have expected fetal DNA to be swamped out by maternal DNA and thus not be detectable, as is discussed below.

Assuming only for argument's sake that Ariosa's position is true—that researchers believed “[m]ost if not all cells in circulation” release DNA into blood—then both maternal and fetal cells would have been expected to release their DNA. Petition at 9. In March 1997, researchers knew that fetal cells in maternal blood were “extraordinarily rare.” Ex. 1011 at 850:2-¶3. Importantly, the ratio of nucleated fetal cells to nucleated maternal cells ranged from 1 per 5×10^6 to 1 per 1×10^8 . Ex. 1025 at 1234:2-¶5 to 1236:1-¶1. Given the 1,000,000 to 100,000,000 fold difference, if only a small percentage of maternal cells released

their DNA (due to normal cell turnover, for example), then the expected ratio of cell-free fetal DNA to cell-free maternal DNA would still be very small. So a researcher would have expected the cell-free maternal DNA to far outweigh the cell-free fetal DNA. A researcher in noninvasive fetal diagnosis thus would not have had a reasonable expectation that the cell-free fetal DNA—that Kazakov speculated *might* be present in maternal blood²⁴—would be abundant enough relative to maternal DNA to successfully be detected using one of Simpson 1994’s methods.

Fourth, Simpson 1994 and the prenatal diagnosis art as a whole taught away from being combined with Kazakov. Kazakov speculated that cell-free DNA in maternal blood might come from fetal trophoblasts. Ex. 1014 at 235:¶1. But Sargent taught that most pregnant women do not have trophoblasts in their peripheral circulation. 2038 at 155:¶3, 159:¶1 (following bullet point text) to 160:¶2. And Simpson 1994 described the many difficulties researchers had encountered in trying to recover trophoblasts from maternal blood. Ex. 1025 at 1230:2:¶2 to 1232:1:2. Thus, a person of ordinary skill in the art of non-invasive fetal diagnosis would have been dissuaded from attempting prenatal diagnostic testing on the Kazakov maternal blood cell-free DNA.

²⁴ Kazakov did not attempt to amplify or detect fetal DNA and had no interest in prenatal diagnosis.

In short, because Schallhammer is not prior art, because a person of ordinary skill in the art would have been dissuaded from combining Simpson 1994 with Kazakov, or because there would have been no reasonable expectation of success in making the combination, Ariosa cannot prevail on its unpatentability ground D.

E. Ariosa’s unpatentability ground E—claims 1-2, 4-5, 8, 19-22, and 24-25 are obvious over Gocke in view of Robbins and Simpson 1994—does not have a reasonable likelihood of prevailing.

Ariosa does not have a reasonable likelihood of prevailing on its unpatentability ground E because (i) Ariosa failed to establish that Gocke’s 102(e) date is earlier than the ’540 patent’s March 4, 1997 priority date, (ii) Ariosa used hindsight reconstruction, (iii) there was no reason to combine the references, (iv) there was no reasonable expectation of success, and (iv) Gocke taught away from combining cancer references with Simpson 1994.

First, as is discussed above, Ariosa did not meet its burden to establish an effective date for Gocke that is earlier than the ’540 patent’s priority date (March 4, 1997). Gocke’s filing date is March 14, 1997, and Ariosa did not establish that Gocke, which is a self-described “continuation-in-part” application, could rely on its earlier applications as supporting the disclosure Ariosa relied on. Petition at 53-57. Thus, Gocke cannot be applied against the ’540 patent claims because Ariosa has failed to meet its burden to show Gocke is prior art.

The following discussion, however, assumes solely for argument’s sake that

Gocke is prior art.

Second, Ariosa used impermissible hindsight reconstruction in combining Simpson 1994 with Gocke and Robbins. *KSR* did not abolish the prohibition against hindsight reasoning: “A flexible TSM test remains the primary guarantor against a non-statutory hindsight analysis.” *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). The starting point for an obviousness determination cannot be the inventor’s disclosed motivation:

Furthermore, the path that leads an inventor to the invention is expressly made irrelevant to patentability by statute.... The only inquiry is whether the teachings ... would have rendered the claimed invention obvious to one of ordinary skill in the art; this inquiry as a matter of law, is independent of the motivations that led the inventors to the claimed invention

Life Tech., Inc. v. Clontech Labs, Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000).

Here, as noted by Ariosa, the ’540 patent cited a Vasioukhin patent that describes testing for cancer mutations in plasma DNA. Petition at 7; Ex. 1008 at ¶54; Ex. 1001 at 1:44-46. The ’540 patent and Lancet 1997 (authored by the inventors and colleagues) also cited publications describing the detection of tumor DNA in patient plasma, and Lancet 1997 stated that these publications “prompted” the investigation into whether fetal DNA could be detected in maternal plasma and serum. Ex. 1001 at 1:38-43; Ex. 1016 at 485:2-¶2. Ariosa has merely used or

replaced the cancer references cited in the '540 patent and in Lancet 1997 with similar cancer references and cobbled together, via its "Technical Background" section and conclusory expert declarations, an obviousness position that is riddled with hindsight.

Ariosa's Petition does not even attempt to identify a reason to combine Gocke or Robbins with Simpson 1994 beyond the bald assertion that Gocke's method *could be* performed on a pregnant woman with choriocarcinoma. Petition at 53 & 55.²⁵ Of course, whether a method *could be* performed is not the standard for establishing obviousness.²⁶ Plus, Ariosa's experts provide no support for the proposition that a woman with choriocarcinoma *would be* pregnant. Ex. 1007 at ¶¶78 & 79; Ex. 1007 at ¶¶ 105 & 120. In fact, choriocarcinoma is not diagnosed in

²⁵ Ariosa's Petition includes none of the reasoning of its experts for its ground E beyond the untrue assertion that a woman with choriocarcinoma would be pregnant. Ariosa should not be able to rely on any reasoning that the Petition itself did not include or even allude to beyond citing the declarations. To permit Ariosa to establish unpatentability only by way of its declarations without establishing it in the Petition would permit Ariosa to skirt the page limits imposed on petitions.

²⁶ Neither Gocke nor Robbins discloses that choriocarcinoma can be diagnosed or screened for using cancer DNA detection. Ex. 1002; Ex. 1021.

women during pregnancy: “[C]horiocarcinoma can *follow* any type of pregnancy.” Ex. 2039 at 355:1-¶2 (emphasis added). Thus, even Ariosa’s attempt at hindsight reconstruction fails.

Third, there was no reasonable expectation of successfully combining Gocke, Robbins, and Simpson 1994. As is discussed above (Section IV.D.), knowledge in the prenatal diagnosis art combined with Ariosa’s theory of DNA release would have led one to believe that cell-free fetal DNA could not be detected because it would be far outweighed by cell-free maternal DNA. Plus, cancer references also provided doubt as to whether even cell-free *tumor* DNA could be successfully detected in patient blood: “[T]here may be problems developing diagnostic and screening tests for early cancer....” Ex. 2040 at 628:2-¶2. For example, many cancer publications discussed the findings that increased cell-free (presumably tumor) DNA mainly occurred in patients with metastatic disease or who had a large tumor load: “[D]etectable amounts of circulating DNA were found only in [27% of cancer] patients [i.e., those] with advanced malignancies bearing a large tumor cell burden.” Ex. 1027 at 711:1-¶1 & 2; Ex. 1019 at 1035:Abstract (29% of patients had detectable microsatellite alterations in cell-free DNA—all having advanced disease). Because of these concerns, researchers proposed only using these detection methods *after* initial diagnosis—for, e.g., assessing tumor burden and predicting future metastases. Ex.

1019 at 1035:Abstract & 1037:1:¶3. The combination of cancer art and fetal diagnosis art, in the absence of the '540 patent's disclosure, would have led an artisan of ordinary skill to conclude that it would *not* have been reasonable in March 1997 to believe that either cancer diagnosis or fetal nucleic acid detection would have been possible using cell-free DNA.

Fourth, Gocke and other cancer references taught away from combining cancer teachings with fetal diagnostic references such as Simpson 1994. Gocke described a number of mechanisms for why cell-free tumor DNA could appear in blood. Ex. 1002 at 3:25-47 (e.g., cancer patients' plasma has inhibitors of DNase and "shedding of phospholipid vesicles from tumor cells is well described"). And Chen suggested that "greater access to the vasculature" in certain cancers led cell-free tumor DNA to be released into circulation. Ex. 2041 at 1033:2:¶3 to 1034:1:¶1. These mechanisms are inconsistent with Ariosa's fetal cell DNA release theory, and they were not applicable to fetal cells in 1997. Petition at 13-14; Ex. 1033 at ¶70.

Thus, because Ariosa failed to show that Gocke is prior art, and because—even if Gocke is prior art—Ariosa failed to establish a reason to combine Gocke or Robbins with Simpson 1994 with a reasonable expectation of success, Ariosa cannot prevail on its unpatentability ground E.

VII. In the unlikely event that Ariosa established *prima facie* obviousness, Isis Innovation's significant objective evidence of nonobviousness rebuts the *prima facie* case.

Ariosa has failed, for both factual and legal reasons, to establish *prima facie* obviousness. But, for argument's sake, Isis provides compelling, objective evidence that warrants finding the '540 patent claims nonobvious: the claimed method (i) received professional acclaim, (ii) satisfied a long-felt, but previously unmet, need and (iii) achieved commercial success.

The Federal Circuit has repeatedly stressed the importance of considering such objective evidence of nonobviousness: "[T]his evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes *independent evidence* of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (emphasis added). Record evidence of nonobviousness is probative and must be given substantial weight. And Isis demonstrates, below, that there is a nexus between the merits of the claimed invention and the objective evidence.

A. Drs. Lo's and Wainscoat's invention has received significant professional acclaim.

A finding of nonobviousness is supported if the claimed invention received professional acclaim and industry approval. *See Vulcan Eng'g Co. v. Fata Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002) (stating that "[a]ppreciation by contemporaries skilled in the field of the invention is a useful indicator of

[nonobviousness]."). The '540 patent's claimed method of non-invasively detecting paternally inherited fetal nucleic acid in maternal plasma or serum has received overwhelming praise and recognition:

- Researchers in prenatal diagnostics have described the method as the "Holy Grail" of prenatal diagnosis and "One of the most exciting discoveries made in recent years that has most prominently influenced the development of new non-invasive alternatives for prenatal diagnosis." Ex. 2015 at 226:1:¶1 & 230:2:¶4; Ex. 2012 at 654:1:¶2.
- The Royal Society described the invention as "creating a paradigm shift in non-invasive prenatal diagnostics." Ex. 2042 at ¶2.
- On September 18, 2012, Dr. Lo received the Illy Tieste Science Prize in human health for his development of, and continued work on, diagnostics based on cell-free fetal DNA in maternal plasma. Ex. 2043.
- According to Google Scholar, Drs. Lo and Wainscoat's Lancet 1997 publication has been cited 1175 times. Ex. 2044:first result:line 6; *see* Petition at 38-41 for correspondence between Lancet 1997 and the claims.

In addition, Sequenom's commercially-available tests embodying the '540 patent's method—the MaterniT21 and MaterniT21 PLUS tests—have received substantial praise in the field. These tests embody essential features present in all claims of the '540 patent and reflecting the merits of the claimed invention:

Paternally-inherited fetal nucleic acid is amplified and detected in maternal plasma or serum samples (i.e., a noninvasive method). Ex. 2045 at 20459:1:¶2 to 2:¶2 (“One end of the clonally expanded copies of each plasma DNA fragment was sequenced ... to detect chrY DNA from plasma of women carrying male fetuses.”).

Examples of praise for the invention include the following. Prior to the MaterniT21 PLUS test development, Dr. Barbara O’Brien, a physician and director of Perinatal Genetics at Women’s & Infants Hospital commended the MaterniT21 test as having “an important place in the plan of care for women who are at a high risk for carrying a child with Down syndrome.” Ex. 2046 at ¶3. Likewise, Dr. Frank Boehm, Vice Chairman of the Department of Obstetrics and Gynecology and Director of Maternal Fetal Medicine at Vanderbilt Center for Women’s Health, stated that “[a]s part of our mission to provide the *best possible medical care* to patients visiting our facility, we are pleased to provide patients with access to Sequenom CMM’s MaterniT21 LDT as an opportunity to gain valuable information early in a woman’s pregnancy.” *Id.* at ¶5 (emphasis added). Importantly, the American College of Obstetricians and Gynecologists (the U.S.’s leading group of physicians providing health care for women) and the Society for Maternal-Fetal Medicine have recommended the use of the Sequenom’s tests. Ex. 2047 at, e.g., ¶1.

The professional acclaim for the ’540 patent’s claimed method demonstrates

a significant, nonobvious advance over the art. *See Vulcan* at 1373 (“The commercial response to an invention is significant to determinations of obviousness....”).

B. The '540 patent satisfied a long-felt, unmet need.

The '540 patent satisfies a long-felt but previously unmet need for a non-invasive fetal DNA detection method, permitting for the first time the use of maternal serum or plasma to detect a paternally-inherited nucleic acid of fetal origin. A finding of nonobviousness is supported if the claimed invention satisfies a long-felt need. *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). Demonstrating a long-felt need requires showing that a need existed as of the filing date of the application and that existing solutions were inadequate. *Id.*

Prior to the invention, there was a long-felt need for a non-invasive method to detect paternally-inherited fetal nucleic acids to reduce risky, invasive testing. Before the '540 patent's priority date, no successful non-invasive fetal nucleic acid *detection* methods existed. The fetal nucleic acid detection methods of amniocentesis and CVS were invasive, and carried risks for the fetus and mother. And the then-existing non-invasive methods did not detect fetal nucleic acid and could merely determine, for example, the *probability* that a woman is carrying a fetus with Down syndrome. Such methods required a significant percentage of

women to undergo confirmation by the *invasive* nucleic acid detection methods due to the false-positive error rate. Ex. 1011 at 847:2:¶2; Ex. 1033 at 33-37. The '540 patent's invention greatly reduces the percentage of women who need to undergo this invasive and risky testing: "If referrals for amniocentesis or [CVS] were based on the sequencing test results [using the '540 patent's claimed method], about 98% of the invasive diagnostic procedures could be avoided." 2022 at 1:Abstract:Conclusion.

Because of the need for a non-invasive fetal nucleic acid detection method, beginning in 1969 and continuing for several decades, researchers actively—but unsuccessfully—pursued techniques using rare fetal cells from maternal blood. Ex. 1024 at 2357:1; ¶1 to 3:¶2. Despite rigorous efforts, no one achieved acceptable results: "An old and so far unfulfilled dream ... is to have a method available which would allow *in utero* diagnosis of genetic anomalies without having to bear procedure-related risks to the mother and/or the fetus." 2006 at 218:1¶1. In the face of unsuccessful results with fetal cells, scientists expressed doubt as to whether non-invasive fetal cell testing would "ever become available as a clinical routine diagnostic test." Ex. 2048 at 519:2:¶5.

Drs. Lo and Wainscoat have succeeded where others have failed. As is discussed in further detail below, the claimed method has been widely successful in providing non-invasive detection methods. By providing non-invasive methods

that successfully detect paternally-inherited nucleic acid of fetal origin, the '540 patent satisfied a long-felt but previously unmet need.

C. The claimed invention is a commercial success that revolutionized the non-invasive prenatal diagnostic market.

The commercial success of the '540 patent reflects the non-obviousness of the claimed invention. *See, e.g., SIBIA Neurosciences, Inc. v Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed. Cir. 2000). Here, the important advance of the claimed invention—a non-invasive method for detecting paternally-inherited fetal nucleic acid—underlies the commercial acquiescence in the '540 patent and the expanding sales of its commercial embodiments. *Cable Electric Products, Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1027 (Fed. Cir. 1985), *vacated and remanded on other grounds*.

Appreciating the '540 patent's "Holy Grail" method for detecting paternally-inherited nucleic acid of fetal origin in maternal serum or plasma, Sequenom voluntarily entered into an exclusive license to the '540 patent. Ex. 2049 at 4:¶5, 5:¶2 & F-27:¶¶1-2. For its exclusive rights to the '540 patent and other intellectual property, Sequenom has paid millions of dollars to Isis and has committed to pay future royalties. *Id.* Likewise, Sequenom has partnered with LifeCodexx AG, a European company, for the commercialization of laboratory testing services in Europe in the field of non-invasive prenatal diagnostics under the corresponding European patent to the same invention. Ex. 2050 at ¶¶1-2.

Given the highly-sought-after technology claimed in the '540 patent, Sequenom invested tens of millions of dollars in the exclusive licensing and development of the '540 patent's method. Under its exclusive license, Sequenom developed the MaterniT21 test—the first U.S. launched non-invasive prenatal diagnostic test for trisomy 21. Ex. 2051 at 440:¶1. Since the initial launch of the MaterniT21 test in mid-October 2011, every quarter has seen a growth in sales volume. Ex. 2052 at ¶¶1-2. More recently, Sequenom developed the MaterniT21 PLUS test, which also detects trisomies 13 and 18 and chromosome Y. Ex. 2047 at 2:¶¶3-4. In early 2012, financial analyst Zarak Khurshid predicted that Sequenom would run 40,000 of the tests in 2012. Ex. 2052 at 2:¶3. In fact, sales through September 2012 have exceeded expectations, and analysts recently revised upwards the 2012 estimate to 50,000 tests. Ex. 2053 at slide 6:point 5. With the expectation of an increasing market demand, Sequenom has increased its run rate to 90,000 per year. *Id.* at slide 20:point 5. This increasing demand for Sequenom's tests evidences the nonobviousness of the '540 patent's claims.

VIII. Conclusion

Because Ariosa lacks standing to petition for IPR in view of its prior district-court challenge to the validity of the '540 patent, the Board should not institute *inter partes* review. Likewise, the Board should not institute IPR because Ariosa's *Prometheus*-based arguments permeate the petition and improperly ask the Board

to decide issues under Section 101. Additionally, the Board should not institute *inter partes* review because Ariosa has not met its burden to show it has a reasonable likelihood of prevailing on any of its grounds of unpatentability as to any claim of the '540 patent. If the Board should institute an IPR, Ariosa's *Prometheus*-based arguments should be stricken and ignored. If the Board does institute IPR, Isis Innovation reserves the right to supplement its arguments as to why Ariosa will not prevail on the merits of its unpatentability challenge.

The Patent Trial and Appeal Board is hereby authorized to charge any fees associated with the *inter partes* review no. 2012-00022 to Deposit Account 19-0036. Our Customer I.D. is 45324.

Respectfully submitted,
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in black ink, appearing to read 'Eldora L. Ellison', with a stylized flourish at the end.

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CERTIFICATION OF SERVICE

The undersigned hereby certifies that the foregoing “ISIS INNOVATION LIMITED’S PRELIMINARY PATENT OWNER RESPONSE PURSUANT TO 37 C.F.R. §42.107(a)” was served on December 31, 2012, in its entirety on the following via Federal Express:

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